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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,820	02/04/2005	Hirotaka Teranishi	Q86059	4002

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EXAMINER	
MCINTOSH III, TRAVISS C	
ART UNIT	PAPER NUMBER
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,820	TERANISHI ET AL.	
	Examiner	Art Unit	
	Traviss C. McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-15,23 and 34-44* is/are allowed.

6)☒ Claim(s) *18,19,21,22 and 25-33* is/are rejected.

7)☒ Claim(s) *16,17,20 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claims 1-14 are directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(B), claims 25-33, directed to the process of making or using an allowable product, previously withdrawn from consideration as a result of a restriction requirement, are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Because all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, **the restriction requirement as set forth in the Office action mailed on 9/22/2006 is hereby withdrawn**. In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Claim Objections

Claims 16-22 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 15. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP

§ 706.03(k). It is noted that the intended use as set forth in claims 16-22 is not seen to be of any patentable import to the composition as claimed, as such, these are seen to be the same as claim 15.

As such, claim 24 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 23. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 27-28 and 32-33 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions and methods of using the claimed pyrazole derivatives, does not reasonably provide enablement for compositions and methods of using the claimed pyrazole derivatives in combination with the other additional agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)***. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:
(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

Claim 29 is drawn to a pharmaceutical combination comprising the pyrazole derivative represented structurally in claim 1 and at least one member of a Markush group which contains a

tremendously large list of functionally described compounds, including insulin sensitivity enhancers, dipeptidyl peptidase inhibitors, amylin agonist, a thyroid hormone receptor agonist, a neutral endopeptidase inhibitor, and urinary alkalinizer, just to name a few. Claims 30 and 31 are drawn to methods of using the combination.

The state of the prior art

Pyrazole derivatives are known in the art to be a SGLT2 inhibitors, as seen by US 7,084,123. The pyrazole derivative is not known to be effectively combined with any other agent. Combination therapy, and drug-drug interactions are known in the art to have various effects, and when physicians use several drugs in combination, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction, and if so, how to take advantage of the interaction if it leads to improvement in therapy or how to avoid the consequences on an interaction if they are adverse. A potential drug interaction refers to the possibility that one drug may alter the intensity of the pharmacological effects of another drug if given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs, or the appearance of new effects which is not seen with either drug alone. The frequency of significant beneficial or adverse effects is unknown. The interaction between the drugs may be pharmacokinetic, i.e. alteration of the absorption, distribution, or elimination of one drug by another, or may be pharmadynamic, i.e. interactions between agonists and antagonists at drug receptors. The most important drug-drug interactions occur with drugs that have serious toxicity and low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences. Additionally, drug-drug interactions can be clinically important if the disease being controlled with the drug is serious or potentially fatal if left

undertreated. Drugs are known to interact at any point during their absorption, distribution, metabolism, or excretion; the result being an increase or decrease in concentration of the drug at the site of action. As individuals vary in their rates of disposition of an given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable, but can be very significant. See Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Medical Publishing Division, 2001, pages 54-56.

The level of predictability in the art

As seen by Goodman & Gilman, the art of combination therapy is unpredictable. Drug-drug interactions are known to be beneficial or adverse, yet there is no way to known until the drugs are actually tested in an individual.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the claims as written. Applicants have not provided any indication of what drugs might be toxic and what the drugs therapeutic indexes are. Applicants have merely listed various drugs in the specification.

The existence of working examples

The working examples set forth in the instant specification are drawn to methods of making various pyrazole derivatives and tests using only those pyrazole compounds. There are no examples using combination therapy. There are no compositions made with multiple agents.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable one to make or use the combination of their pyrazole derivative and any of the thousands of possibly agents without undue experimentation. It is noted that the specification should teach how to make and use the invention, not teach how to figure out for oneself how to make and use the invention. See ***In re Gardner, 166 USPQ 138 (CCPA 1970).*** In order to practice the instant invention, one of ordinary skill in the art would be confronted with the undue burden to first determine if a drug actually performed any of the functionally described activities (i.e., test a compound to see if it is a insulin sensitivity enhancer, or a glucose absorption inhibitor, or an insulin secretion enhancer, etc.). If the skilled artisan did determine if the drug had the activity, then they would be required to determine whether the drug would interact with the pyrazole derivative, first *in vitro*, and then *in vivo*. And if the drug did interact, the artisan would be required to determine how they interacted, did the interaction provide adverse effects or beneficial effects, or produce completely new effects? They would be required to determine at what point in the patients system the effect occurred, and determine what is needed to ensure the patient was effectively treated. One of skill in the art would not be able to use the invention as instantly claimed without undue experimentation as the art recognizes the unpredictability of drug-drug interactions.

Claims 18, 19, 21, 22, 25, and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the various conditions, does not

reasonably provide enablement for prevention of diseases associated with hyperglycemia or diseases associated with increased blood galactose levels, such as for example, diabetes or obesity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The breadth of the claims - The nature of the invention

Claims 18, 19, 21, 22, 25, and 30 are drawn to compositions for and methods of preventing diseases associated with increased blood galactose levels and preventing diseases associated with hyperglycemia comprising administering the pyrazole compounds of claim 1. It is noted that due to the voluminous nature of the specification, the examiner was not able to locate where in the specification the phrase "diseases associated with hyperglycemia" is defined, and as such, the examiner is reading these in the broadest reasonable construction consistent with the art in light of the specification. Hyperglycemia is known to be elevated glucose levels in the blood. The art recognizes things related to diabetes and hyperglycemia includes accelerating the hardening and narrowing of the arteries, leading to strokes, coronary heart diseases, and other blood vessel diseases. Additionally, diabetes is known to be the third leading cause of death in the United Additionally, diseases associated with hyperglycemia can include various diseases such as obesity, Syndrome X, ketoacidosis, hypertriglyceridemia, hypertension, and diabetes to name a few.

The state of the prior art

Plasma glucose is normally filtered in the kidney in the glomerulus and actively reabsorbed in the proximal tubule. SGLT2 appears to be the major transporter responsible for

the reuptake of glucose at this site. The SGLT specific inhibitor phlorizin or closely related analogs inhibit this reuptake process in diabetic rodents and dogs resulting in normalization of plasma glucose levels by promoting glucose excretion without hypoglycemic side effects. Long term (6 month) treatment of Zucker diabetic rats with an SGLT2 inhibitor has been reported to improve insulin response to glycemia, improve insulin sensitivity, and **delay the onset of nephropathy and neuropathy** in these animals, with no detectable pathology in the kidney and no electrolyte imbalance in plasma. Selective inhibition of SGLT2 in diabetic patients would be expected to normalize plasma glucose by enhancing the excretion of glucose in the urine, thereby improving insulin sensitivity, and **delaying the development of diabetic complications**. Ninety percent of glucose reuptake in the kidney occurs in the epithelial cells of the early S1 segment of the renal cortical proximal tubule, and SGLT2 is likely to be the major transporter responsible for this reuptake. SGLT2 is a 672 amino acid protein containing 14 membrane-spanning segments that is predominantly expressed in the early S1 segment of the renal proximal tubules. The substrate specificity, sodium dependence, and localization of SGLT2 are consistent with the properties of the high capacity, low affinity, sodium-dependent glucose transporter previously characterized in human cortical kidney proximal tubules. In addition, hybrid depletion studies implicate SGLT2 as the predominant Na^+/glucose cotransporter in the S1 segment of the proximal tubule, since virtually all Na-dependent glucose transport activity encoded in mRNA from rat kidney cortex is inhibited by an antisense oligonucleotide specific to rat SGLT2. Studies strongly implicate SGLT2 as the major renal sodium-dependent transporter of glucose. Inhibition of SGLT2 would be predicted to reduce plasma glucose levels via enhanced glucose excretion in diabetic patients. O-aryl glycosides are known to be a SGLT2

inhibitors, as seen by US Patent 6,683,056. Additionally, the art is silent with respect to one compound being able to prevent diseases associated with hyperglycemia such as obesity, diabetes, Syndrome X, and hypertension as well as prevent diabetic complications such as atherosclerosis, coronary heart disease, and death.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the scope of claim as written. The examiner notes, there has not been provided sufficient instruction or sufficient methodological procedures to support the alleged efficacy of prevention instantly asserted.

The existence of working examples

The working examples set forth in the instant specification are drawn to various methods of preparing the claimed compounds, to methods of assaying the inhibitory effects on human SGLT activity, and to determining the amount of glucose excreted after administration of the compounds. There has been no experiments on humans or any animal models which would provide evidence of preventing any condition.

There has not been provided sufficient evidence which would warrant the skilled artisan to accept the data and information provided in the working examples as correlative proof that a healthy individual would never become afflicted with the claimed conditions if subjected to the instantly claimed therapy.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the use of the pyrazole compounds to prevent the development of diseases associated with hyperglycemia, such as diabetes and obesity, without undue experimentation. The teaching of SGLT inhibitors only being capable of **delay** the onset of nephropathy and neuropathy and **delaying** the development of diabetic complications above is further evidence the art does not recognize SGLT inhibitors as capable preventative pharmaceuticals. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation.

Reasonable guidance with respect to preventing any condition relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of the condition. This type of data might be derived from widespread genetic analysis or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug treatment and subsequent knowledge of the prevention of the disease is the essence of verification of a valid preventive agent.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-28 and 30-33 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25-26 and 30-31 are indefinite wherein the claims are drawn to methods of treating various things, but fail to state to whom the compositions are intended to be administered. Add the phrase, to a subject in need thereof would be seen to obviate the instant rejection.

Claim s 27-28 and 32-33 provides for the use of the claimed pyrazole compounds, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Allowable Subject Matter

Claims 1-15, 23, and 34-44 are allowed.

The prior art is not seen to teach or fairly suggest the compounds claimed. The closest art available is seen to be US 2006/0128635 – which teaches aryl groups in my applications Q or T position, wherein my application is drawn to alkyl or cycloalkyl groups located there, which is not the same as aryl groups, as evidenced by the definition on page 35 of the instant specification as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl groups.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C. McIntosh whose telephone number is 571-272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Traviss McIntosh
March 31, 2007

Shaojia A. Jiang
Supervisory Patent Examiner
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